

## **REMARKS**

### ***Status of the Claims***

Upon entry of the instant amendment, claims 1 and 7-17 will be pending in the above-identified application and stand ready for further action on the merits.

In this Amendment, claims 1 and 15 have been amended without prejudice or disclaimer of the subject matter contained therein. New claims 16 and 17 have been added.

Claims 1 and 15 have been amended as indicated in the Advisory Action to delete the term "toluene" and to replace the phrase "an alcohol" with "methanol." Support for amended claims 1 and 15 and new claims 16 and 17 can be found at least at page 12, lines 1-22, and Examples 1-6 of the present Specification. No new matter has been introduced by way of the instant Amendment.

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### ***Advisory Action***

It was asserted in the Advisory Action dated February 19, 2010, that the claims submitted in the Amendment filed February 5, 2010, are not fully supported with regard to the recitation of the reaction solvents tetrahydrofuran, toluene, or a solvent mixture of toluene and an alcohol for processes where the reaction solvent has a volume 7 to 10 times the volume of a compound having structural formula (III).

While Applicants respectfully disagree with this assertion, in order to expedite prosecution of the present application, Applicants have amended the claims to recite the reaction solvents tetrahydrofuran or a solvent mixture of toluene and methanol. It was conceded in the Advisory Action that processes comprising the reaction solvents tetrahydrofuran and a mixture of toluene and methanol, wherein the reaction solvent has a volume 7 to 10 times the volume of a compound having structural formula (III), are supported by the Specification.

***Claim Rejections under 35 U.S.C. § 112, first paragraph***

Claims 1 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the phrase “in a reaction solvent of toluene in which appropriate quantities of soluble solvent is added” is said to introduce new matter.

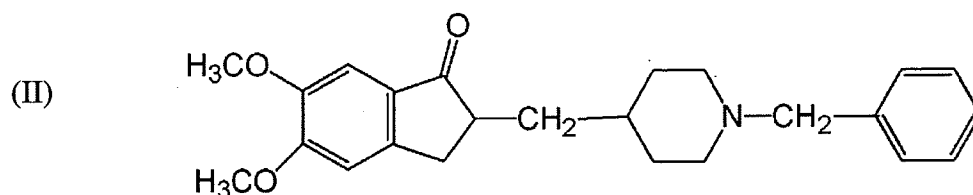
Applicants have amended claims 1 and 15 to delete reference to “appropriate quantities” and to better define the composition of the reaction solvent, in order to obviate this rejection. As pointed out above, support for the amendments to claims 1 and 15 can be found at least at page 12, lines 1-22, and Examples 1-6 of the present Specification. As discussed below, the volume ratios for volume reaction solvent to amount of compound having structural formula (III) in Examples 1-6 of the present application are 8:1, 7:1, 8:1, 7:1, 8:1, and 7:1, respectively. Further support for such amendments at pages 9-10 and 13 of the Specification was pointed out by the Examiner at pages 2 and 3 of the Office Action. Thus, in view of the discussion above, Applicants respectfully request that the rejection of claims 1 and 15 under 35 U.S.C. § 112, first paragraph, be withdrawn.

***Claim Rejections under 35 U.S.C. § 103***

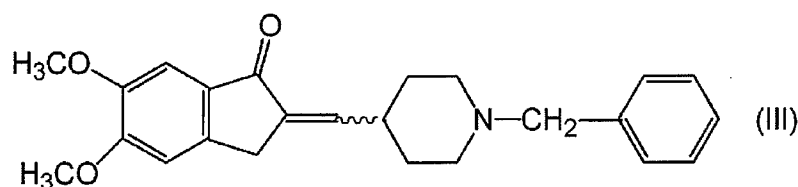
Claims 1 and 7-15 are rejected under 35 U.S.C. § 103(a) over JP-A-179151 (*hereinafter referred to as D1*)(supplemented with the corresponding patent US 4,898,841) or JP-61-187674 (*hereinafter referred to as D3*)(supplemented with its English Abstract CA118).

*D1 and D3 taken alone or together do not teach a process with a Raney nickel catalyst in a reaction solvent of tetrahydrofuran or a solvent mixture of toluene and methanol, with a volume ratio of between 7:1 (7 times) and 10:1 (10 times) for reaction solvent to a compound having structural formula (III).*

*D1 and D3 taken alone or together do not teach a process for preparing a compound of the structural formula (II):*



in the presence of a Raney nickel catalyst in a reaction solvent of tetrahydrofuran or a solvent mixture of toluene and methanol, wherein the reaction solvent is 7 to 10 times the volume of the compound of the structural formula (III)



as in the claimed invention.

As previously pointed out by the Examiner, **DI** does not disclose any specific catalytic reaction processes using a Raney nickel catalyst, although Example 4 teaches production of a compound of structural formula II using a catalytic reduction with a palladium-carbon catalyst. (Example 1 teaches production of a compound having a structure similar to that of formula II with a rhodium-carbon catalyst.) Thus, **DI** does not teach a volume ratio of between 7:1 (7 times) and 10:1 (10 times) for volume reaction solvent to amount of compound having structural formula (III), as in the claimed invention.

Example 4 of **DI** discloses reacting 0.4 g of a compound of the structural formula (III) in 16 ml of reaction solvent (*e.g.*, methylene chloride:methanol), and thus the approximate volume ratio in Example 4 is 40:1 (40 times). Example 1 of **DI** does not teach a compound of the structural formula (III) or the product of the claimed invention, however it has a volume ratio of reaction solvent to reactant of 27:1.

Volume ratios for reaction solvent to a compound having structural formula (III) taught by *D1* and *D3* are much higher than those of the claimed invention, although the product yields are similar to those of the claimed invention.

The volume ratios for Examples 1 and 4 of *D1* are much higher than those of the claimed invention, which are between 7:1 and 10:1. (The volume ratios for volume reaction solvent to amount of compound having structural formula (III) in Examples 1-6 of the present application are 8:1, 7:1, 8:1, 7:1, 8:1, and 7:1, respectively.) Furthermore, the product yields of Examples 1-6 (82.8%, 76.6%, 80%, 74.9%, 81.5%, and 94.6%, respectively) of the present application and that for Example 4 (82%) of *D1* are comparable. (Again, the product of Example 1 of *D1* is not the same as that of the claimed invention.) This is important, because a smaller volume of reaction solvent is used and then removed in the claimed process for a given amount of product, as compared to the volume of reaction solvent used and then removed for the specific catalytic reduction process taught by *D1*. As stated above, *D1* does not teach or suggest the volume ratio range of reaction solvent to compound of the structural formula (III) recited in the pending claims.

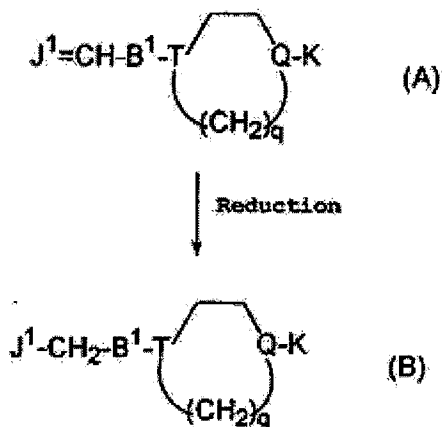
*D3* does not teach a Raney nickel catalyst as in the claimed invention. As previously pointed out by the Examiner in the Office Action mailed March 24, 2009, *D3* discloses the use of ruthenium catalysts. Still further the volume ratio of reaction solvent to the reactant (*e.g.*, compound of the structural formula (III)) in all of the examples of *D3* is 15:1, which is outside the range of the claimed invention, while the yields (85.4%-87%) are also similar to those of Examples 1-6 of the present application.

Thus, as with *D1* above, a smaller volume of reaction solvent is used and then removed in the claimed process for a given amount of product, as compared to the volume of reaction solvent used and then removed for the specific catalytic reduction processes taught by *D3*. As stated above, *D3* also does not teach or suggest the volume ratio range of reaction solvent to compound of the structural formula (III) recited in the pending claims of between 7:1 (7 times) and 10:1 (10 times).

Thus, taken alone or together *D1* and *D3* do not teach each and every element of the claimed invention, as they do not teach the volume ratio range for reaction solvent to compound of the structural formula (III) of between 7:1 and 10:1. Applicants respectfully request that the rejection of claims 1 and 7-15 under 35 U.S.C. § 103(a) be withdrawn.

It would not have been obvious to one of ordinary skill in the art at the time the invention was made to combine a Raney nickel catalyst with the claimed reaction solvents in the recited volume ratios.

In addition, while *D1* teaches the generic reduction reaction



may be carried out using “a catalyst such as a catalyst of palladium and carbon, Raney nickel and a catalyst of rhodium and carbon” (US 4,495,841, col. 21, line 68 to col. 22, line 3), it does not specify which reaction solvents should be used with particular catalysts and reactants. Examples 1 and 4 of *D1*, discussed above, both use tetrahydrofuran (THF) as a reaction solvent, but neither example uses a Raney nickel catalyst and Example 1 does not produced the claimed product.

One of skill in the art at the time the claimed invention was made would be aware of the technical difficulties associated with using a Raney nickel catalyst in a reaction solvent of THF or a solvent mixture of toluene and methanol. It is well known in the art that a Raney nickel catalyst will spontaneously ignite if it becomes dry. (See attached MSDSs for Raney nickel catalyst labeled Exhibits 1 and 2.)

Therefore, at the time the invention was made there were serious concerns about the safety of using a Raney nickel catalyst in THF or a solvent mixture of toluene and methanol in large-scale industrial production methods. In fact, when Applicants tried to engage a company that specializes in catalytic reduction processes to perform the claimed methods, the company declined citing the combination of Raney nickel catalyst and THF as being too dangerous (due to concerns that flammable THF might be ignited by dried Raney nickel catalyst). It is common knowledge in the art that Raney nickel catalyst should be preserved in water or alcohol, because it is likely to ignite spontaneously when it dries. For this reason Raney nickel catalyst is usually used with an alcohol.

Thus, although Raney nickel catalysts are used in the selective reduction of olefins and *DI* separately discloses Raney nickel catalyst as one possible catalyst and THF as a reaction solvent with other catalysts, one of ordinary skill in the art at the time the invention was made would not have been motivated to combine a Raney nickel catalyst with THF or a solvent mixture of toluene and methanol, as suggested by the Examiner. Instead one of skill in the art would have been motivated to select an alcohol as a reaction solvent with a Raney nickel catalyst.

This assertion is further supported by two references cited in the International Search Report, CHEN, X. *Asymmetry*, 2002, Vol. 13, No. 1, pp. 43-46 and OGAWARA, "Gosei Shiyaku," 1980, Kodansha Ltd., page 313, which disclose the use of a Raney nickel catalyst with ethanol for reduction reactions, but not THF or a solvent mixture of toluene and methanol, as in the claimed invention. In view of the safety concerns associated with Raney nickel catalysts, one of ordinary skill in the art at the time the invention was made would have been motivated to choose a catalyst (such as a palladium catalyst) that is more manageable in industrial processes.

Furthermore, the ratio volume of reaction solvent to compound of the structural formula (III) in the claimed invention is even more non-obvious, as the claimed combination of reactant (*e.g.*, compound of the structural formula (III)), reaction solvent (*e.g.*, compound of the structural formula (III)) and Raney nickel catalyst by itself would not have been obvious to one of skill in the art at the time the claimed invention was made.

As explained above, Raney nickel catalyst can spontaneously ignite when it becomes dry. Thus, for safety reasons, it is important to ensure that Raney nickel catalyst is stored in liquid. In fact, Raney nickel catalyst is sold as slurry in water and/or alcohol. The claimed methods use relatively smaller volumes of reaction solvent to produce the compound of the structural formula (II) than methods disclosed by the cited art. One of ordinary skill in the art would not have been motivated to use smaller reaction solvent volumes with a Raney nickel catalyst than those used with other catalysts in the cited art, because of safety concerns. By decreasing the volume of reaction solvent, one of skill in the art would expect the risk of unintentionally permitting the Raney nickel catalyst to dry and ignite to be increased (especially in a manufacturing environment where flammable solvents like THF are present).

The purity of donepezil produced by the unobvious combination of a Raney nickel catalyst and THF or a solvent mixture of toluene and methanol, with a volume ratio of reaction solvent to compound of structural formula (III) of between 7:1 and 10:1 is unexpected.

The claimed methods permit production of high-purity donepezil that can be obtained without purification steps being necessary after the reduction reaction. The donepezil produced by the claimed methods (including a Raney nickel catalyst and THF or a solvent mixture of toluene and methanol) can be used directly in preparing its hydrochloride salt without intervening purification steps. This added benefit of using the Raney nickel catalyst with compound of the structural formula (III) and THF or a solvent mixture of toluene and methanol in the volume ratios recited in the claims would not have been obvious to one of skill in the art at the time the invention was made based on the cited art.

Data taken from Table 1 on page 18 of the Specification is reproduced below for the Examiner's convenience. Example 1 in Table 1 shows that the purity of a hydrogenated reaction solution (free donepezil) is as high as 99.6%, and that of the final product is 99.8%. Thus, additional purification (such as crystallization) after the reductive reaction has little effect. The degree of purity of free donepezil produced using the claimed methods would not have been obvious to one of skill in the art at the time the invention was made.

Examples 1-6 represent working examples of the claimed invention and produce free

donepezil of higher purity than Examples 7-9, which employ alcohol and/or ethyl acetate reaction solvents, not the THF or a solvent mixture of toluene and methanol, as recited in the claims. Furthermore, reference Examples 1-3, which combine THF with rhodium-carbon or palladium-carbon catalysts produce free donepezil having a much lower degree of purity than Examples 1-6, which are directed to the claimed invention.

In Example 6 of the present Specification, the reaction product was not crystallized before being reacted with hydrochloric acid to produce donepezil hydrochloride. Thus, high purity donepezil hydrochloride can be prepared without column chromatography or isolation of the initial reduction reaction product by crystallization as is common with other catalyst systems.

The degree of product purity achieved is due to the unexpected selectivity of the Raney nickel catalyst when used with THF or a solvent mixture of toluene and methanol with the volume ratios of reaction solvent to reactant recited in the claims.

Table 1

Test Sample	Hydrogenated Reaction Solution Purity (%)
Example 1	99.6
Example 2	99.0
Example 3	99.1
Example 4	99.4
Example 5	99.1
Example 6	99.0
Example 7	96.5
Example 8	95.8
Example 9	97.8
Reference Example 1	85.8
Reference Example 2	91.5
Reference Example 3	75.2

As Applicants have previously explained, the degree of purity indicated in Table 1 for products of the claimed methods is higher than the degree of purity achieved by methods taught

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in **D3**, for example, while the product yields remain similar. Thus, the claimed process is more efficient than those taught by the cited art.

To further support this position, Applicants attached a report (**Exhibit 3**) entitled “**Donepezil reaction mixture HPLC results of Commercial batches (384 kg scale)**.” The data in Exhibit 3 is for the years 2007-2009, and the reactions were conducted with a Raney nickel catalyst in THF, where the volume of THF relative to the volume of the compound of the structural formula (III) was about 7:1 or 8:1, as in the claims. As the data shows, the average purity of free donepezil was 99.849% with a standard deviation of 0.010. The purity of the product produced by the claimed methods is very consistent. Furthermore, the amount of undesirable de-benzylated byproduct produced is very low, when compared to processes described in the cited art. It is unexpected that during production of donepezil on a large-scale (384 kg) that such a high degree of selectivity/purity could be achieved by using a Raney nickel catalyst and THF with the volume ratio of reaction solvent and reactant recited in the claims.

In view of the discussion above, Applicants respectfully request that the rejection of claims 1 and 7-15 under 35 U.S.C. § 103(a) be withdrawn.

### CONCLUSION

Based upon the amendments and remarks presented herein, the Examiner is respectfully requested to issue a Notice of Allowance clearly indicating that each of the pending claims 1 and 7-17 is allowable under the provisions of Title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Stephanie A. Wardwell, Ph.D., Reg. No. 48,025 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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Enclosures: Two MSDSs for Raney nickel catalyst (Exhibits 1 and 2) (total 8 pages)  
Donepezil reaction mixture HPLC results of Commercial batches (384 kg scale)  
(Exhibit 3) (2 pages)

  
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